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Gestational hypercalciuria causes pathological urine calcium oxalate supersaturations

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Gestational hypercalciuria causes pathological urine calcium oxalate supersaturations. Although normal pregnant women are more hypercalciuric than women with calcium oxalate nephrolithiasis (243 ± 23 mg/day vs. 194 ± 5 mg/day), pregnancy is not an established stone-forming state and pregnant women do not exhibit pathological crystalluria. One hypothesis to explain their lack of overt stone formation and pathological crystalluria is that pregnancy does not raise urine supersaturation with respect to stone forming salts such as calcium oxalate or calcium monohydrogen phosphate (brushite) to levels as high as in stone forming women. To test this hypothesis, we studied eleven normal women during each trimester of pregnancy, and between six and eight weeks post-partum. During pregnancy, hypercalciuria occurs with unchanged urine volume, citrate and magnesium excretions do not increase proportionally with calcium excretion, and urine pH increases. Supersaturations with respect to calcium oxalate (CaOx) and brushite (Br) are as high as those of women with calcium nephrolithiasis. The lack of pathological crystalluria and stones during pregnancy is not due to a failure of supersaturations to increase; urinary potential for crystallization is as high as in patients with established stone disease.

Normal pregnancy causes hypercalciuria. For example, one study [1] reports the mean calcium excretion of 12 women as 430 ± 15 mg/24 hr, a second [2] reports median values during the first, second, and third trimesters, respectively of 233, 329 and 305 mg/24 hours, and in a third study [3], mean calcium excretion was 313 ± 44 mg/24 hr. By comparison, normal women who are not pregnant excrete 112 ± 7 (SEM) mg/day [4] when eating uncontrolled diets, and few normal women excrete more than 250 mg/24 hours [5, 6]. Gestational hypercalciuria may arise from increased serum levels of 1,25 dihydroxyvitamin D (calcitriol) [7, 8], a hormone that stimulates intestinal calcium absorption [9], and can cause normocalcemic hypercalciuria when given to normal men [10]. In one study [7], serum calcitriol levels (pg/ml) were high during all three trimesters [7] (94 ± 11, 118 ± 9 and 117 ± 11 vs. 51 ± 5 post-partum; all pregnancy values $P < 0.05$ vs. post-partum), and urine calcium levels also were high: 247 ± 54, 316 ± 42, 300 ± 61 mg/24 hour vs. 91 ± 18, for the three trimesters versus post-partum.

As a rule, hypercalciuria causes crystalluria and kidney stones [11–13]. Idiopathic hypercalciuria, a familial and probably hereditary trait [13] that can arise from excessive intestinal calcium absorption, impaired renal tubule calcium reabsorption [5], and calcitriol excess [14, 15] is a common putative cause of calcium oxalate nephrolithiasis. Primary hyperparathyroidism, sarcoidosis, immobilization, glucocorticoid excess, and vitamin D intoxication all cause hypercalciuria and calcium oxalate stones [15–18]. Sarcoidosis is of particular interest here, as calcitriol excess causes hypercalciuria [19, 20]. Hypercalciuria with alkaline urine pH causes calcium phosphate stones, as found in Type I renal tubular acidosis [17, 21–23]. The final common pathway for stone formation in hypercalciuric states is excessive urinary supersaturation with respect to calcium salts [24–26]. Hypercalciuria alone raises mainly calcium oxalate supersaturation [25]; elevated urine pH raises calcium phosphate supersaturations as well [27].

Gestational hypercalciuria is an exception to the rule; pregnancy is not a stone forming condition [28, 29], abnormal crystalluria is not a recognized clinical finding [28, 30], and stone formers who become pregnant do not increase their stone production rate [29]. An obvious hypothesis is that gestational hypercalciuria, unlike other forms of hypercalciuria, is benign because it does not supersaturate the urine with calcium oxalate and calcium phosphate salts. We have tested this idea, and present evidence to the contrary; gestational hypercalciuria raises urinary calcium oxalate and brushite supersaturations to levels of women with established recurrent calcium nephrolithiasis, so normal pregnant women should be at a high risk for pathological crystalluria and kidney stone disease. The lack of stones and overt crystalluria despite high supersaturations implies that pregnancy induces special and presently undefined defenses against crystallization, that deserve a proper study.

Methods

Subjects

We studied 11 women (age 26 to 35 yr, mean 29 ± 3 years) who had no known diseases and used no medications except prenatal supplements. Gestation was uncomplicated except for an intrauterine death from abruptio placentae near term (39 to 40 weeks) in one woman whose fetus had a short, tangled

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Table 1. Values for serum and urine chemistries for normal pregnant women, normal women, and calcium stone-forming women

	Normals	First	Second	Third	Post-P	CaOx	CaPhos
Serum							
Sodium *mEq/liter*	139 ± 0.2	136 ± 0.3[c]	137 ± 0.4[c]	137 ± 0.4[c]	140 ± 0.5	140 ± 0.2[c]	140 ± 0.4
Magnesium *mg/dl*	1.97 ± 0.01	1.93 ± 0.03	1.93 ± 0.03	1.87 ± 0.03[a]	2.01 ± 0.03	1.97 ± 0.01	1.99 ± 0.02
Uric Acid *mg/dl*	3.99 ± 0.12[c]	2.71 ± 0.16[c]	2.99 ± 0.27[b]	3.61 ± 0.34	4.25 ± 0.36	4.24 ± 0.05	3.69 ± 0.14
Phosphorus *mg/dl*	3.52 ± 0.06	3.61 ± 0.09	3.32 ± 0.08	3.30 ± 0.12	4.07 ± 0.14[b]	3.41 ± 0.02	3.38 ± 0.08
Creatinine *mg/dl*	0.82 ± 0.01[c]	0.65 ± 0.01[c]	0.64 ± 0.02[c]	0.67 ± 0.03[c]	0.84 ± 0.03	0.78 ± 0.01[b]	0.78 ± 0.02
Potassium *mEq/liter*	3.92 ± 0.03	3.98 ± 0.1	3.93 ± 0.04	3.95 ± 0.07	4.23 ± 0.11[a]	4.00 ± 0.03	4.08 ± 0.06
Calcium *mg/dl*	9.40 ± 0.03	9.24 ± 0.10	8.86 ± 0.09[c]	8.82 ± 0.07[c]	9.47 ± 0.10	9.45 ± 0.02	9.47 ± 0.04
Urine							
Volume *ml/day*	1215 ± 66	1364 ± 92	1511 ± 130	1504 ± 145	1442 ± 170	1336 ± 35	1752 ± 12[c]
Sodium *mM/day*	127 ± 44	146 ± 10	167 ± 17[a]	125 ± 15	130 ± 13	128 ± 2	130 ± 7
Calcium *mg/day*	112 ± 7	238 ± 20[c]	256 ± 24[c]	235 ± 25[c]	75 ± 12[a]	194 ± 5[c]	244 ± 4[c]
Calcium *mg/C_{Cr}*	0.81 ± 0.05	1.46 ± 0.15[b]	1.45 ± 0.14[b]	1.38 ± 0.16[b]	0.56 ± 0.08[a]	1.38 ± 0.03[c]	1.49 ± 0.10[c]
Creatinine clearance	153 ± 4	168 ± 8	178 ± 6[a]	176 ± 10[a]	133 ± 6[a]	143 ± 2[a]	144 ± 4
Potassium *mM/day*	48 ± 2	55 ± 5	65 ± 5[a]	66 ± 7[a]	65 ± 6[a]	46 ± 1	51 ± 3
Magnesium *mEq/day*	83 ± 5	109 ± 7[b]	130 ± 10[c]	117 ± 7[c]	84 ± 5	80 ± 2	82 ± 3
Uric Acid *mg/day*	540 ± 16	524 ± 40	651 ± 44[a]	687 ± 50[a]	473 ± 337	509 ± 7	548 ± 25
Phosphorus *mg/day*	677 ± 20	666 ± 63	665 ± 65	733 ± 54	758 ± 56	713 ± 11	766 ± 33[a]
Oxalate *mg/day*	26 ± 8	28 ± 2	32 ± 3[a]	33 ± 2[a]	26 ± 2	27 ± 1	34 ± 2[c]
Citrate *mg/day*	699 ± 42	731 ± 34	933 ± 92[a]	986 ± 87[b]	567 ± 58	505 ± 18[c]	380 ± 59[c]

Abbreviations are: post-P, post-partum values; CaOx and CaPhos refer to patients who form such stones; C_{Cr} creatinine clearance in liters/24 hour; mg/C_{Cr}, mg/liter creatinine clearance.
[a] Differs from normals, $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$

umbilical cord. One woman developed asthma during mid-trimester of pregnancy, required oral theophylline, inhaled sympathomimetic drugs, and oral prednisone, but delivered a healthy baby at 32 weeks gestation. Although two women were breast feeding during our post-partum studies, their values did not differ from the rest of the post-partum group and are merged in the group means. Two women with abnormal pregnancies, one with a hydatidiform mole and one with an anephric fetus, were also studied.

In a separate protocol we determined the relationship between urine citrate and calcium, and response of urine calcium and citrate to alkali loading in four normal women age 23 to 29 (mean 26 ± 3 years) eating controlled diets [31, 32].

Study during pregnancy

Blood and urine were obtained once in each trimester of pregnancy, and at six to eight weeks post-partum. Urine studies, only, were done before and after evacuation of a hydatidiform mole in an 18-year-old patient and at approximately 24 weeks gestation in a 25-year-old primigravida with an anephric fetus. All subjects collected 24-hour urine samples while eating their individual diets as out-patients; blood was drawn at the end of the collection period between 7:30 and 9:00 a.m. Because of morning sickness, not all subjects were fasting since the preceding midnight as is our usual practice [16]. Sodium, potassium, uric acid, calcium, phosphorus, magnesium, and creatinine were measured in blood and urine, and oxalate, citrate, sulfate, chloride, and pH, along with volume, in urine only. Supersaturations were calculated using an iterative computer program [33].

Controlled diet alkali study

Four normal women were studied in the Clinical Research Center (CRC). The basic diet contained 60 mEq sodium, 60 mEq potassium, 400 to 500 mg calcium, 200 mg magnesium, and

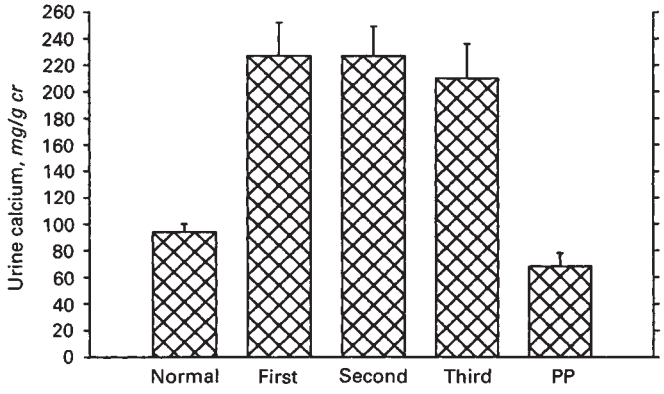

Fig. 1. *Urine calcium excretion during pregnancy exceeded the mean value from our 77 normal women, and post-partum values for the 11 subjects, P < 0.01 all comparisons, all three trimesters.*

700 to 800 mg phosphorus. During control periods, we added 140 mEq NaCl to the diet; for alkali loading, we replaced the 140 mEq of NaCl with sodium bicarbonate. Subjects began each diet seven days before admission to the CRC. Control or alkali diet was started first or second, at random. Subjects were admitted to the CRC on the morning of day 8 of the diet period, continued on the diet for four additional days during testing, and were discharged on day 12. Twenty-four hour urine collections were obtained on days 8 through 11, blood was drawn only on days 8 and 11. Calcium, magnesium, creatinine, sodium, potassium, and bicarbonate were measured in blood and urine. Oxalate, citrate, and sulfate were measured in urine only, and supersaturations were calculated using a computer program [33]. On day 11, arterialized venous blood was drawn for ionized calcium, venous pH and pCO_2. After at least a two

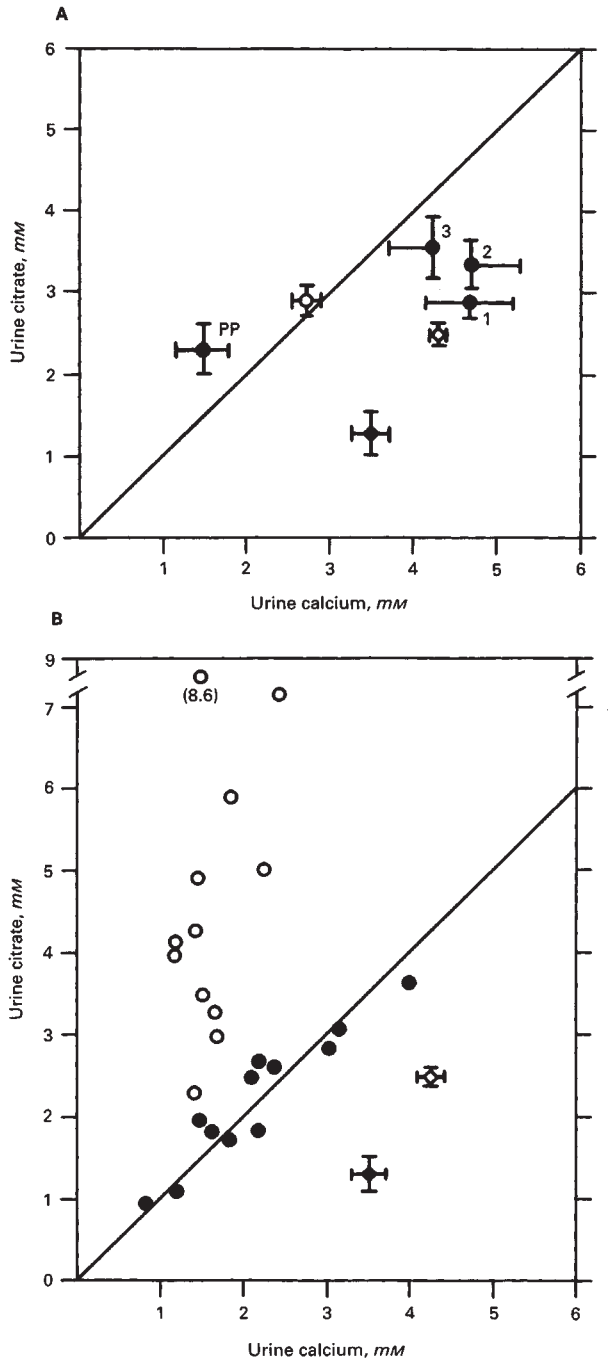

Fig. 2. *Urine citrate and calcium concentrations during pregnancy* (**A**) *and in 4 women eating controlled diets* (**B**). Citrate to calcium ratio was below the line of identity (Diagonal line, both panels) for all three trimesters (numbered closed circles, panel A), and rose above 1 post-partum (pp, A). Open circle in A shows double mean ±SEM for our (4) outpatient normal women. Open and closed diamonds, both panels show data for female calcium oxalate and calcium phosphate stone formers, respectively. Open and closed circles in B show values for alkali supplement and control conditions, respectively, for 4 normal women eating controlled diets and studied in our clinical research center.

week interval with no dietary constraints the alternate diet was started and the 11 day protocol was repeated.

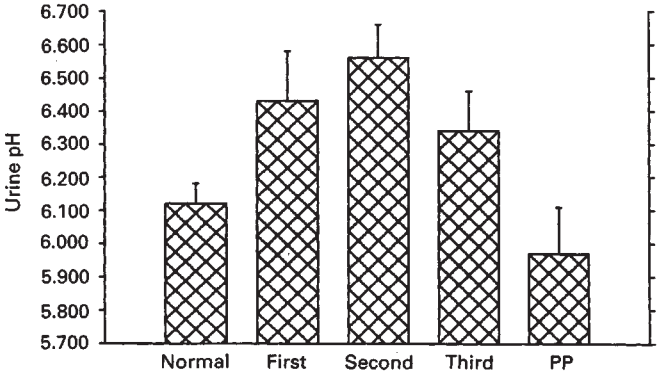

Fig. 3. *Urine pH values during pregnancy were not different from those of our female calcium phosphate stone-formers (6.29 ± 0.09), and exceeded the mean from our 67 normal women, from our female calcium oxalate stone-formers (6.04 ± 0.03) and post-partum values,* P *< 0.01, all comparisons.*

Measurements

Sodium and potassium were measured by flame photometry (Instrumentation Laboratory, Lexington, Massachusetts, USA), inorganic phosphorus and creatinine by autoanalyzer (Technicon Instruments Corp., Tarrytown, New York, USA), calcium and magnesium by atomic absorption spectrophotometry (Video 22, Instrumentation Laboratory), chloride by electrochemical titration (Buchler-Cotlove Chloridometer, Buchler Instruments, Inc., Fort Lee, New Jersey, USA), uric acid by the uricase method [34], urinary sulfate by turbidometry [35], citrate using citrate lyase [36], and oxalate by zinc reduction [37]. Urine pH was measured by pH meter (Beckman 071, Beckman Instruments, Inc., Fullerton, California, USA). Blood gas determinations were done on a Radiometer Blood Micro System (The London Company, Cleveland, Ohio, USA), and blood ionized calcium was by calcium electrode (Nova 2, Nova Biochemical, Newton, Massachusetts, USA).

Calculations and analysis of data

Supersaturations were calculated using an iterative computer model of the relevant ionic interactions in urine and expressed as the ratio of the concentration of calcium oxalate or brushite salt in urine to its own solubility [33]. This ratio is called the relative supersaturation ratio (RSR). Free calcium ion concentration also was calculated by the program. Comparisons between groups used *t*-tests without assumption of equal variances in the two groups [38]. All data are ±SEM.

Results

Normal pregnancy

Throughout pregnancy, urine calcium excretion (Figure 1, Table 1) exceeded values for normal women, and was greater than or equal to values of women with recurrent stone disease (Table 1). Total serum calcium decreased throughout gestation and increased post-partum reaching levels of normal non-gravid women within the first six weeks (Table 1); creatinine clearance was above normal throughout pregnancy, as expected, and calcium excretion was above normal expressed per liter of creatinine clearance.

Although citrate and calcium excretions both increased dur-

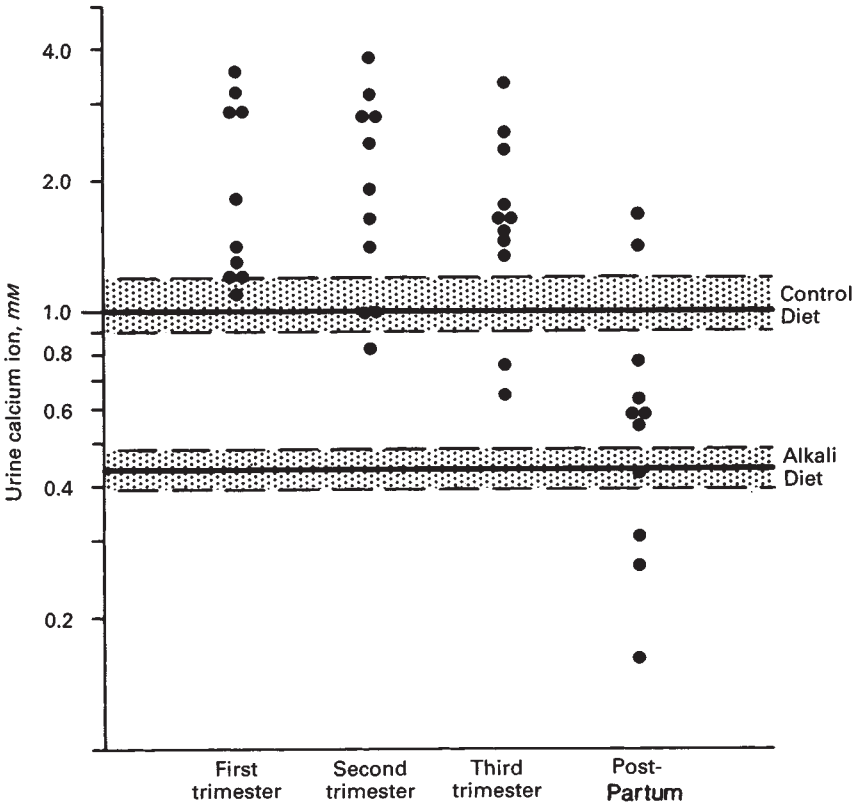

Fig. 4. *Calculated urine calcium ion concentrations during pregnancy exceeded normal values for the 4 normal women eating control and alkali supplemented diets, and post-partum values;* $P < 0.01$, *all comparisons.* Labelled crosshatched bands are ± 2 SEM.

ing pregnancy, urine calcium increased more than urine citrate (Fig. 2A). In healthy non-pregnant women under outpatient conditions we [4] have reported that urine citrate and calcium are equimolar; our mean values are reproduced on Figure 2A as the open circle, and the equimolar line—of identity—is drawn as well. During all three trimesters, urine citrate concentrations were less than calcium concentrations (Fig. 2A), and the departure of the citrate to calcium ratio from 1.0, which is the distance of each point from the line of identity, was similar to what we [4] have observed in women with established calcium oxalate stone disease (open diamond). During the first trimester, the departure was as extreme as in 35 patients we have studied who formed calcium phosphate stones (closed diamond), because citrate excretion hardly increased (Table 1) whereas hypercalciuria was extreme (Fig. 1, Table 1). Post-partum, the citrate to calcium ratio rose above normal.

The low urine citrate to calcium ratio during pregnancy is particularly abnormal when compared to the responses of the four normal women we studied eating controlled diets. Without supplemental alkali, they excreted citrate and calcium in equimolar amounts (Fig. 2B, closed circles). Mean urine pH was 6.188 (0.1 SEM). Given alkali, they increased their citrate excretions, so their citrate to calcium molar ratio was in excess of 2.0 (Fig. 2B, open circles); as expected urine pH rose, to 7.941 (0.06 SEM). The alkali loading data are relevant because urine pH increases during pregnancy (Fig. 3) to values as high as, or above those of women with calcium phosphate stones (legend to Fig. 3). In other words, citrate failed to increase in parallel with calcium excretion during pregnancy, even though urine pH rose, whereas during alkali loading citrate increases even though calcium excretion does not.

Hypercalciuria in excess of hypercitricuria increased calculated urinary free calcium ion concentration (Fig. 4) to levels above those observed post-partum, or in our four normal women eating the control or alkali supplemented diet. By contrast, alkali loading actually reduced urine calcium ion concentration (compare shaded regions on Fig. 4). As a result of the increased free calcium ion level, calcium oxalate supersaturation was above normal (Fig. 5A). Because urine pH and calcium ion concentration both were elevated, brushite supersaturation increased (Fig. 5B), whereas brushite supersaturation did not rise (legend to Fig. 5) when women were given alkali.

Serum sodium and uric acid decreased in first trimester, and remained low (Table 1). Mean urinary volumes during pregnancy and post-partum were similar to those in normal and stone forming women. Magnesium excretion was increased throughout gestation. In the four women studied in the CRC, arterialized venous pH and PCO_2 values were 7.403 ± 0.006 and 38 ± 1 before, and 7.413 ± 0.01 and 40 ± 1 after alkali loading.

Abnormal pregnancy

The woman with the anephric fetus (not illustrated) was hypercalciuric (233 mg calcium/day) and her citrate excretion was 534 mg/day, yielding a citrate to calcium molar ratio of 0.47. Her urine supersaturations for calcium oxalate and brushite were 7.64 and 2.95, respectively (both $P < 0.001$ vs. normals). The patient with the hydatidiform mole also had hypercalciuria, 291 mg calcium/day, that decreased to 178 mg/day by the fifth day after evacuation of the mole. Her initial citrate excretion was 527 mg/day with a citrate to calcium molar ratio of 0.38 and calcium oxalate and brushite supersaturations

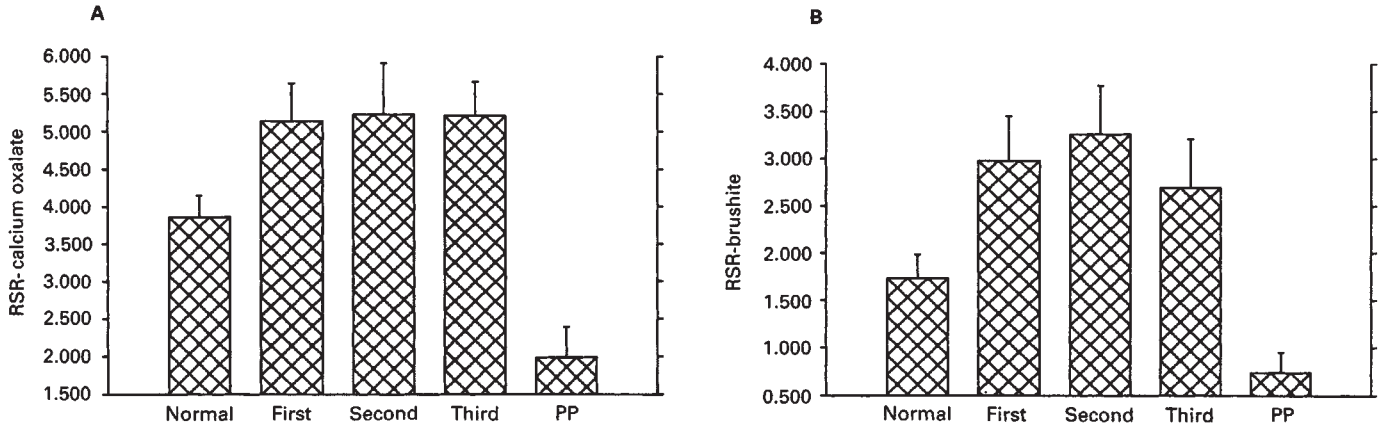

Fig. 5. *Relative supersaturation ratios for calcium oxalate (A), and brushite (B) exceeded our normal mean values, post-partum values, and corresponding values for the 4 normal women studied with (1.24 ± 0.12, brushite, 2.17 ± 0.39, calcium oxalate) and without (1.19 ± 0.24, brushite, 3.34 ± 0.37, calcium oxalate) alkali loading, respectively;* $P < 0.01$, *all comparisons.*

of 10.8 and 9.35, respectively, both $P < 0.001$ versus normals. Five days after removal of the mole, her calcium oxalate and brushite supersaturations were 6.91 and 6.55, respectively, both $P < 0.001$ versus normals, but decreased from levels prior to evacuation.

Discussion

Our principal new finding is that gestational hypercalciuria elevates urine supersaturations with respect to calcium oxalate and brushite, two stone forming salts [39, 40]. Supersaturation is as high as in women with established calcium stone disease and, if our patients have been well chosen, appears universal. The only prior evidence for increased supersaturations in pregnancy is in abstracts [31, 32]. The main factor raising calcium oxalate and calcium phosphate supersaturation is gestational hypercalciuria itself; also important is a decrease in the citrate to calcium molar ratio from the normal of one to a ratio of less than one, because urine citrate excretion rises less than calcium excretion. Brushite supersaturations are further increased by elevated urine pH that is well known [41, 42] and has been ascribed [41] to renal compensation for the chronic respiratory alkalosis of pregnancy.

The hypercalciuria of normal pregnancy has been known since at least 1943 [43]. Increased glomerular filtration rate and calcium filtration [1], and excess intestinal calcium absorption due to high circulating levels of calcitriol [7] both are possible mechanisms. Our study of the patient with the hydatidiform mole suggests that the placenta is sufficient to cause hypercalciuria. The decrease in total serum calcium level we observed has been described by others [44] and seems due to a decrease in plasma albumin with normal ionized calcium [45–47]. Glomerular filtration rate increased in the first trimester and remained elevated until delivery, as others describe [48, 49]. The serum calcium change, and increased GFR do not seem related to the hypercalciuria.

Given that urine calcium oxalate and brushite supersaturations are as high in pregnancy as in patients with established calcium nephrolithiasis, why has pathological crystalluria not been an obvious clinical finding, and why is stone formation not a commonly recognized complication of pregnancy? One possible explanation is simply that pregnancy lasts only nine months; though all of the pregnant women in, for example, any given year accumulate many years at risk, no one woman is exposed to increased supersaturations for more than nine months at a time. Perhaps short duration is also why malignancy usually is not a stone forming state despite severe hypercalciuria [50]. Even so, many women have multiple pregnancies and therefore have cumulative hypercalciuria of several years duration, yet multigravidas are not recognized as being at increased risk for calcium stones [28].

Another explanation is an increase of protective mechanisms, perhaps some "inhibitor" of crystallization. Magnesium is an inhibitor of calcium oxalate crystal growth [51], and its excretion increases in pregnancy but not as much as calcium excretion. Other inhibitors of stone formation such as acidic glycoproteins [52, 53] may increase during pregnancy and play a protective role, and we have presented preliminary evidence to support this notion [54]. No detailed study of the matter has been reported.

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